

Remarks**Specification**

Applicants have amended the Title to more specifically relate to the claimed invention as described in the Specification.

Claims

A new set of claims clearly based on the written description and closely patterned after the amended claims are submitted to more clearly and patentably distinguish over the prior art. Examiner's withdrawal of rejections based on 35 USC 112 is noted.

Claim Rejections – 35 USC § 103

In the Office Action dated May 8, 2009, Examiner continued to reject pending claims under 35 USC § 103 based on an extensive combination of references including Giao, EP Abstract, White, and Lai et al. Examiner states that the claims are *prima facie* obvious over the combination of references and further that there are deficiencies in the Inventors' Declaration under 37 CFR 1.132 which do not overcome the obviousness rejections.

Applicants respectfully traverse these rejections as they might be applied to the new set of claims and submits that the new claims are not *prima facie* obvious over the prior art, alone, or in any combination, and, moreover, that the Supplementary Declaration overcomes the Examiner's previous grounds of rejection.

Lack of *prima facie* obviousness

Giao et al. discloses a four way combination of dihydroartemisinin, piperaquine, trimethoprim and primaquine for the treatment of malaria. Applicants' revised composition claims are clearly and patentably distinguished over Giao et al since applicants' claims are now limited to artemisinin (not dihydroartemisinin), piperaquine, and primaquine plus formulation adjuvants. The phrase "consisting essentially of" clearly excludes other active ingredients such

as trimethoprim which is an essential ingredient of Gao et al's composition and present in Gao in relatively large ratios. Lai et al pertains to cancer treatments and does not establish the functional equivalence of dihydroartemisinin in the treatment of malaria. In addition the teaching of Klayman cited by Examiner show that dihydroartemisinin is a more potent derivative than artemisinin for malaria treatment. Hence Klayman leads away from applicants' selection of artemisinin in a three way combination with primaquine and a super low dose of primaquine where the objective is to shorten the course of treatment and get reduced side effects.

Expressed in different words, Klayman would not motivate the person of ordinary skill in the art to employ artemisinin in place of the more potent derivative, dihydroartemisinin, and have a reasonable expectation of reducing the dosing treatment. In fact, one might expect the opposite effect. In addition, the effect of removal of trimethoprim from the Gao et al treatment regimen renders the effect of applicants' new combination unpredictable. From the sparse extract of data in Gao et al, it should be noted that about 35 hours on average are required for treatment with Gao's proposed trimethoprim containing formula while Applicants' treatments may be accomplished in 24 hours.

The White reference (Phil Trans R Soc Lond B 1999, 354,739-749) by Examiner clearly points out the importance of malaria treatments of low cost and ready availability and that malaria is the top parasitic infectious disease deserving great attention from the medical arts. However, White does not show or suggest the novel and unpredicted ratio of artemisinin, primaquine, and low dose of primaquine which Applicants discovered and which leads to short, efficacious, less toxic, and less costly treatment of this dreaded disease.

The references in combination or alone clearly do not render applicants' amended claims unpatentable.

The Supreme Court's opinion in KSR reminds us that while there is no rigid rule for determining motivation or suggestion in the prior art, reasonable predictability is still required based on the prior art. In a subsequent opinion in *Takeda v. Alphapharm* 492. F. 3d1350 (Fed. Cir. 2007), the Federal Circuit reminds us that detailed and specific findings are required to support obviousness rejections and that generalizations are not sufficient. Applying those cases to the present situation, one would observe that none of the references alone or in combination

point to the applicants' empirical discovery of the claimed ratios employing artemisinin, instead of the more costly and thought to be more potent derivatives thereof.

Moreover, the present inventive combination and ratios are demonstrated to be advantageous over those in the prior art references.

The Supplementary Declaration

Examiner raised several points in respect of the initial Declaration in finding that document not persuasive in overcoming the rejection of the claims. These points are as follows:

- The test populations and amount of each component in the tested combinations are not specified;
- Prior claim 1 allowed for the presence of zero primaquine;
- The dosing was not sufficiently explicit;
- There are no statistical data to exclude overlap or lack of statistical significance of the proof of lower side effects.

The Supplementary Declaration submitted herewith is respectfully submitted to overcome each of Examiner's points and more clearly place the claims in condition for allowance.

More specifically in regard to the Supplementary Declaration, it is clearly pointed out that 716 and 106 patients suffering from pernicious malaria were treated by the formulation of the present invention and the prior art, respectively. For the present invention, a total dose of 1750mg (4 tablets) in two doses over 24 hours was employed where the present formulation of each tablet consisted of 62.5 mg of artemisinin, 312.5 of piperaquine, and 2 mg of primaquine. For the prior art formulation, a total dose of 2880 mg (8 tablets) in four doses over 32 hours was employed where each tablet comprised 40 mg of dihydroartemisinin and 320 mg of piperaquine phosphate. Statistical analyses shown in Table 1 of the Supplementary Declaration confirms the statistical significance of the reduced level of side effects for the claimed ratios of ingredients according to the present invention. Quite importantly, the doses were such that the curative rates

according to the selected doses were both acceptably high and not significantly different from a practical medical standpoint at 97.7 % for the present invention and 98.2% for the prior art.

For these reasons, we respectfully submit, that applicants have shown that the unpredicted ratio of ingredients claimed for malaria treatment, surprisingly and unexpectedly accomplishes treatment of human patients suffering from malaria infection with less side effects and less suffering than prior treatments. Moreover, the direct use of artemisinin instead of a derivative thereof, primaquine and a very low dose of primaquine is more affordable as is required by developing populations subject to malarial infection. It is unpredicted and not obvious that the formulation of the present invention would be effective to control pernicious malaria in patients at significantly shorter times of administration and about 1/3 less dose than the reference formulation. Hence it could not be predicted that the present formulation could treat such patients in a more cost effective manner with statistically significantly less side effects and accompanying discomfort than the reference formulation.

For these reasons the amended claims are not obvious and a notice of allowance is courteously solicited.

Telephone communication with the Examiner

Applicants' undersigned attorney spoke with Examiner Arnold by telephone October 28, 2009 regarding Applicants' RCE filed September 8, 2009 and submission of a Supplemental Declaration and accompanying amendment. Examiner Arnold confirmed that the proper procedure is to submit these documents as soon as possible prior to the end of the six-month statutory period for his further consideration. Examiner Arnold's courtesy and actions are gratefully acknowledged. Accordingly, applicants believe no fee is due with this response. However, if any fee is due for any reason to maintain the pendency of the RCE, the USPTO is hereby authorized and requested to charge our Deposit Account No. 03-2775, under Order No. 13796-00002-US from which the undersigned is authorized to draw.

Respectfully submitted,

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